SUMMARY OF PRODUCT CHARACTERISTICS

Betahistine dihydrochloride, tablet, 24 mg

1. NAME OF THE MEDICINAL PRODUCT

Serc 24 mg Tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 24 mg betahistine dihydrochloride equivalent to 15.63mg**.** For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

A round, biconvex, scored, white to almost white tablet with bevelled edges. The diameter is 10 mm; the tablet weight is about 375 mg. The inscription is 289 on either side of the score on one tablet-side. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ménière's Syndrome as defined by the following triad of core symptoms:
- vertigo (with nausea/vomiting)
- hearing loss (hardness of hearing)
- tinnitus

4.2 Posology and method of administration

Posology
The recommended initial daily dosage is 24mg betahistine.
In case that this dosage is not sufficient, the maximum daily dosage can be increased to 48 mg betahistine.

When the maximum daily dosage of 48 mg is indicated, adults take one 24 mg tablet twice a day (in the morning and in the evening).
The dosage should be individually adapted according to the response.

Paediatric population:
Betahistine 24 mg tablets are not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Geriatric population:
Although there are limited data from clinical studies in this patient group, extensive post marketing experience suggests that no dose adjustment is necessary in this patient population.

Renal impairment:
There are no specific clinical trials available in this patient group, but according to post-marketing experience no dose adjustment appears to be necessary.

Hepatic impairment:
There are no specific clinical trials available in this patient group, but according to post-marketing experience no dose adjustment appears to be necessary.

Method of administration
Preferably during meals, with some water.

Duration of treatment
Improvement can sometimes only be observed after a couple of weeks of treatment. The best results are sometimes obtained after a few months. There are indications that treatment from the onset of the disease prevents the progression of the disease and/or the loss of hearing in later phases of the disease.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Phaeochromocytoma.

4.4 Special warnings and precautions for use

Patients with bronchial asthma and history of peptic ulcer need to be carefully monitored during the therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed. Based on *in vitro* data no *in vivo* inhibition on Cytochrome P450 enzymes is expected.

In vitro data indicate an inhibition of betahistine metabolism by drugs that inhibit monoamino-oxidase (MAO) including MAO subtype B (e.g. selegiline). Caution is recommended when using betahistine and MAO inhibitors (including MAO-B selective) concomitantly.

As betahistine is an analogue of histamine, interaction of betahistine with antihistamines may in theory affect the efficacy of one of these drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of betahistine in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant therapeutic exposure. As a precautionary measure, it is preferable to avoid the use of betahistine during pregnancy.

Lactation
It is not known whether betahistine is excreted in human milk.
Betahistine is excreted in rat milk. Effects seen post-partum in animal studies were limited to very high doses.The importance of the drug to the mother should be weighed against the benefits of nursing and the potential risks for the child.

Fertility
Animal studies did not show effects on fertility in rats.

4.7 Effects on ability to drive and use machines

Betahistine is indicated for Ménière's syndrome defined by the triad of core symptoms vertigo, hearing loss, tinnitus. The disease can negatively affect the ability to drive and use machines. In clinical studies specifically designed to investigate the ability to drive and use machines betahistine had no or negligible effects.

4.8 Undesirable effects

The following undesirable effects have been experienced with the below indicated frequencies in betahistine-treated patients in placebo-controlled clinical trials [very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)].

Gastrointestinal disorders
Common: nausea and dyspepsia

Nervous system disorders
Common: headache

In addition to those events reported during clinical trials, the following undesirable effects have been reported spontaneously during post-marketing use and in scientific literature. A frequency cannot be estimated from the available data and is therefore classified as "not known".

Immune System disorders
Hypersensitivity reactions, e.g. anaphylaxis

Gastrointestinal disorders
Mild gastric complaints (e.g. vomiting, gastrointestinal pain, abdominal distension and bloating). These can normally be dealt with by taking the dose during meals or by lowering the dose.

Skin and subcutaneous tissue disorders
Cutaneous and subcutaneous hypersensitivity reactions, in particular angioneurotic oedema, urticaria, rash, and pruritus.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

A few overdose cases have been reported. Some patients experienced mild to moderate symptoms with doses up to 640 mg (e.g. nausea, somnolence, abdominal pain).
More serious complications (e.g. convulsion, pulmonary or cardiac complications) were observed in cases of intentional overdose of betahistine especially in combination with other overdosed drugs.
Treatment of overdose should include standard supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-vertigo preparations. ATC-Code: N07CA01

Mechanism of action
The mechanism of action of betahistine is only partly understood. There are several plausible hypotheses that are supported by animal studies and human data:

- Betahistine affects the histaminergic system:
  Betahistine acts both as a partial histamine H1 receptor agonist and histamine H3-receptor antagonist also in neuronal tissue, and has negligible H2-receptor activity. Betahistine increases histamine turnover and release by blocking presynaptic H3-receptors and inducing H3-receptor downregulation

- Betahistine may increase blood flow to the cochlear region as well as to the whole brain:
  Pharmacological testing in animals has shown that the blood circulation in the striae vascularis inner ear improves, probably by means of a relaxation of the precapillary sphincters of the microcirculation of the inner ear. Betahistine was also shown to increase cerebral blood flow in humans.

- Betahistine facilitates vestibular compensation:
  Betahistine accelerates the vestibular recovery after unilateral neurectomy in animals, by promoting and facilitating central vestibular compensation; this effect characterized by an up-regulation of histamine turnover and release, is mediated via the H3 Receptor antagonism. In human subjects, recovery time after vestibular neurectomy was also reduced when treated with betahistine.

- Betahistine alters neuronal firing in the vestibular nuclei:
  Betahistine was also found to have a dose dependent inhibiting effect on spike generation of neurons in lateral and medial vestibular nuclei.

Pharmacodynamic effects
The pharmacodynamic properties as demonstrated in animals may contribute to the therapeutic benefit of betahistine in the vestibular system.

Clinical efficacy and safety
The efficacy of betahistine was shown in studies in patients with vestibular vertigo and with Ménière's disease as was demonstrated by improvements in severity and frequency of vertigo attacks.

5.2 Pharmacokinetic properties

Absorption
Orally administered betahistine is readily and almost completely absorbed from all parts of the gastro-intestinal tract. After absorption, the drug is rapidly and almost completely metabolized into 2-pyridylacetic acid. Plasma levels of betahistine are very low. Pharmacokinetic analyses are therefore based on 2-PAA measurements in plasma and urine.

Under fed conditions Cmax is lower compared to fasted conditions. However, total absorption of betahistine is similar under both conditions, indicating that food intake only slows down the absorption of betahistine.

Distribution
The percentage of betahistine that is bound by blood plasma proteins is less than 5 %.

Biotransformation
After absorption, betahistine is rapidly and almost completely metabolized into 2-PAA (which has no pharmacological activity).
After oral administration of betahistine the plasma (and urinary) concentration of 2-PAA reaches its maximum 1 hour after intake and declines with a half-life of about 3.5 hours.

Elimination
2-PAA is readily excreted in the urine. In the dose range between 8 and 48 mg, about 85% of the original dose is recovered in the urine. Renal or fecal excretion of betahistine itself is of minor importance.
Linearity/non-linearity
Recovery rates are constant over the oral dose range of 8 – 48 mg indicating that the pharmacokinetics of betahistine are linear, and suggesting that the involved metabolic pathway is not saturated.

5.3 Preclinical safety data

Chronic toxicity
Adverse effects in the nervous system were seen in dogs and baboons after intravenous doses at and above 120 mg/kg.
Chronic oral toxicity testing for 18 months in rats at a dose of 500 mg/kg and 6 months in dogs at a dose of 25 mg/kg showed betahistine to be well tolerated with no definitive toxicities.

Mutagenic and carcinogenic potential
Betahistine does not have mutagenic potential.
In an 18 months chronic toxicity study in rats betahistine up to a dose of 500 mg/kg did not show any evidence for carcinogenic potential.

Reproduction toxicity

Effects in reproductive toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betahistine 24 mg tablets contain microcrystalline cellulose, mannitol (E421), citric acid monohydrate, colloidal anhydrous silica and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Betahistine dihydrochloride tablets are supplied in packages containing 20, 50, 60, 100 tablets, packaged in press-through blister strips of PVC/PVDC and grey aluminium lidding foil of 10 or 20 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY